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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,236	11/30/2000	Russell J. Linderman	5051.509	4373

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MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,236	LINDERMAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of the paper filed 8/26/03, claims 1, 8, 9 have been amended, and claims 2, 4-7, 10-60 cancelled. Claims 1, 8 and 9 are pending.

Applicants' arguments filed 8/26/03 have been considered and found persuasive in part. The previously imposed §112, second paragraph rejections are withdrawn.

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8, 9 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, the specification proposes that the compounds (to which the claims are drawn) inhibit insect propagation by a process in which esterase biosynthesis is inhibited by a process which begins with stimulation of the TMOF receptor. However, there is no evidence that the TMOF receptor is affected one way or another by the compounds, or that esterase biosynthesis is affected one way or another by the compounds. In addition, it remains unknown at this time whether insect propagation is in any way altered.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As is evident to the skilled entomologist who is endeavoring to discover effective insecticides, structure/activity relationships are unpredictable, and many insects are resistant. The following references disclose that insects develop resistance. Some of the references disclose that increased esterase activity is one of the mechanisms:

Lee, Sung-Eun (*Agricultural Chemistry and Biotechnology* **44**(3), 105-112, 2001)

Field, L. M. [Biochemical Sites of Insecticide Action and Resistance (2001), 209-219. Editor(s): Ishaaya, Isaac. Publisher: Springer-Verlag, Berlin, Germany]

Devorshak, Christina (*Reviews in Toxicology (Amsterdam)* 2(7,8), 501-537, 1998)

Wilkins, R. M. (*Brighton Crop Protection Conference--Pests and Diseases* (vol. 2), 511-516, 1998)

Feyereisen, R. (*Toxicol. Lett.* (1995), 82/83(1-6), 83-90, 1995)

In addition to the foregoing, the following references disclose either(a) that compounds may be highly effective against some insects, but not others, or (b) that minor structural

changes can eliminate activity:

- Inoue (USP 4752417) discloses (col 1, line 19+) that a change at one chiral center can eliminate insecticidal activity.

- Wolfe(USP 4,342,176) discloses (col 2, line 58) that a given insecticide may be highly active against one insect species and inactive against another.

- Stehrer-Schmid, Paula (*Mutation Research* **339**(1), 61-72, 1995) discloses that three 2,3-dihydro-2,2- dimethylbenzofuran derivs. without a carbamate function are inactive.

- Kay, I. R. (*Crop Prot.* **12**(4), 310-14, 1993) discloses that Diazinon, carbofuran and dimethoate were ineffective against the eggfruit caterpillar (*Sceliodes cordalis*).

- Yamauchi, Satoshi (*Biosci., Biotechnol., Biochem.* **56**(11), 1760-8, 1992) discloses that the 3,4-dimethoxyphenyl analog was totally inactive, even at a high dose level.

- VanWagenen, Bradford C. (*J. Org. Chem.* **58**(2), 335-7, 1993) discloses that a structurally related compound, di-Me N2-creatininylphosphate (II), was inactive in the insecticidal screens.

- Yoshikawa, Hiromichi (*Biosci., Biotechnol., Biochem.* **56**(9), 1467-9, 1992) discloses that the 6-nitro derivs. were completely inactive as insecticides.

- Kole, Ramen K. (*J. Agric. Food Chem.* **40**(7), 1208-10, 1992) discloses that rotenone was very active, but dehydrorotenone was found to be completely inactive

- Dhingra, Swaran (*J. Entomol. Res.* **14**(2), 139-41, 1990) discloses that lindane and malathion were ineffective against the mealy bug.

- Mitsudera, Hiroyuki (*Nippon Noyaku Gakkaishi* **16**(3), 387-95, 1991) discloses analogs of nereistoxin that are insecticides. Also disclosed is that minor structural changes eliminated activity.

    - Carmellino, M. L. (*Boll. Chim. Farm.* **129**(5), 190-4, 1990) discloses insecticidal activity of quinolinecarboxylic acids, as well as minor structural

variants that are inactive.

In addition, the specification proposes that the compounds may act by stimulating the TMOF receptor. Each of the following references discuss the issue of receptor activation (or receptor antagonism) versus *in vivo* activity. As is evident, the relationship between the two is "unpredictable":

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith, "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor

activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

Accordingly, "undue experimentation" would be required to determine which, if any, of the disclosed compounds can be used to inhibit esterase biosynthesis or to inhibit propagation of mosquitos.

In the response filed 8/26/03, it is argued that "no incredible utility issues" are involved in controlling mosquitos. However, the examiner has not argued that utility for the claimed invention is lacking. Instead, the issue is whether the specification teaches the skilled artisan "how to use" the disclosed compounds to inhibit propagation of mosquitos under the precepts of 35 USC §112, first paragraph.

In the response filed 8/26/03, it is argued that the level of skill is high. This argument was also made in the response filed 12/18/02, and the argument addressed

in the response mailed 2/25/03. As indicated in that Office action, if the obstacles to success are insurmountable, no level of skill will be sufficiently high to overcome them. If a given genus of compounds is not effective to inhibit propagation of mosquitos (to begin with), no amount of skill on the part of an experienced entomologist will be sufficient to find conditions under which the compounds will inhibit propagation of the insects. It is true, as argued in the response filed 8/26/03, that the skilled entomologist would be able to design experiments which could determine whether or not the disclosed compounds could inhibit propagation of mosquitos, but the question is that of the amount of experimentation required to achieve success (i.e., inhibition of propagation), not the amount of experimentation required to achieve absence of success (i.e., no inhibition).

Next, the response asserts that none of the references previously cited by the examiner (Office action mailed 2/25/03) provides a basis to doubt the objective enablement of reducing insect populations using the compounds recited in claim 1. However, each of the references cited in the previous Office action (mailed 2/25/03) supports the conclusion of unpredictability in the pursuit of efficacious insecticides. For example, each of Inoue, Wolfe, Stehrer-Schmid, Kay, Yamauchi, VanWagenen, Yoshikawa, Kole, Dhingra, Mitsudera, and Carmellino amply

supports the conclusion that minor changes in structure of an insectide can lead to elimination of activity, or else that a given compound may inhibit propagation of one species of insect, yet be ineffective against other species. It may be true that there exist (unclaimed) compounds which will inhibit propagation of mosquitos, but it is also true that very minor changes in the structures of those compounds can lead to elimination of activity. It is possibly true that one can no more predict elimination of activity than retention of activity, but the point is that the skilled entomologist cannot predict insecticidal activity merely by viewing the structure of a compound. The case for unpredictability is on firm ground, and the response filed 8/26/03 provides no specific reason why the skilled entomologist would believe that the activity (or absence of activity) of a given compound can be predicted merely by viewing the structure of it on paper. In addition to the foregoing, as indicated previously, there are no working examples, and no direction or guidance as to how to use the disclosed compounds to reduce a population of mosquitos.

In accordance with the foregoing, "undue experimentation" would be required to determine which, if any, of the claimed compounds can be used to inhibit esterase biosynthesis or to inhibit propagation of mosquitos.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

D. Lukton 12/10/03

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher S. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600